

REMARKS

Claims 1-15 are pending in the current patent application. Applicants gratefully acknowledge the withdrawal of the previous objection to claim 1 and the withdrawal of the previous rejections under 35 USC §112, 1st paragraph; 35 USC §112, 2nd paragraph; and 35 USC §102(b) in view of the previous response.

The 35 USC §103(a) Rejection

I. Claims 1-15 were rejected under 35 USC §103(a) as allegedly being obvious over O'Conner et al (US Patent 6,448,225 issued on 9/10/02) in view of Patel (US Patent 5,358,708 issued on 10/25/94).

Applicants respectfully traverse this rejection. The Examiner has stated that O'Conner teaches a stable aqueous formulation of human growth hormone (hGH) comprising hGH, a citrate, phosphate, Tris, succinate or histidine buffer (2 mM to 50 mM, providing pH 5.5 to 7), non-ionic surfactant, polyethylene polymer, tonicity agent and preservative and that the formulation is stable upon storage for 6 to 18 months at 2 to 8 °C. The Examiner has admitted that O'Conner does not teach formulations of human growth hormone that also comprise methionine. The Examiner then stated that Patel teaches aqueous formulations of an interferon, a granulocyte-macrophage colony stimulating factor or an interleukin also comprising methionine. The Examiner then alleges that one of ordinary skill in the art would be motivated to modify O'Conner by incorporating the methionine used in Patel to achieve the allegedly predictable result of a stable liquid formulation with extended storage lifetime of any polypeptide, thus rendering the instantly claimed invention prima facie obvious.

Applicants respectfully disagree with this conclusion. The instantly claimed invention is directed to a formulation of human growth hormone comprising methionine and a polymer stabilizer. Applicants respectfully submit proper combination of O'Conner and Patel does not provide the instantly claimed invention and thus does not render it obvious. Neither O'Conner or Patel teach the use of the polymer stabilizer in conjunction with methionine as required by the instantly claimed invention. The polymer stabilizer required in the instantly claimed invention is selected from a polyethylene glycol or polyethylene glycol derivative (see instant specification at page 17 paragraph [0044]). O'Conner teaches the use of certain non-ionic surfactants such as a polysorbate, a poloxamer, polyols or ethylene/polypropylene block polymers. O'Conner does not disclose the use of a polyethylene glycol as a polymer stabilizer. Patel teaches an

interferon, a granulocyte-macrophage colony stimulating factor or an interleukin in an aqueous buffer also comprising methionine or histidine or a mixture thereof but makes no mention whatsoever of the use of a polymer stabilizer such as a polyethylene glycol or polyethylene glycol derivative. Proper combination of O'Conner and Patel does not result in a formulation comprising human growth hormone, methionine and a polymer stabilizer as instantly claimed and thus the instantly claimed invention is non-obvious in view of these references.

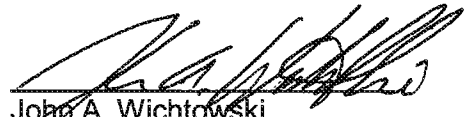
Applicants also submit that one of ordinary skill in the art would not be motivated to modify the combination of O'Conner and Patel to arrive at the instantly claimed invention since there is no motivation to do so. The obviousness rejection is based on combination of Patel et. al., which references the use of methionine as a stabilizer without the use of a polymer stabilizer for the following proteins: interleukin, interferon, and granulocyte macrophage colony stimulating factor with the O'Conner hGH formulation which lacks both the polymer stabilizer and methionine. One of ordinary skill in the art would not be motivated to modify the combination of O'Conner and Patel since the use of methionine as a stabilizer is not only protein specific, but can also be pH specific and is therefore methionine is not known as a common stabilizer. The literature also discloses that the use of methionine as a stabilizer is very dependent upon the protein and the conditions of the formulation. In fact, even the use of methionine in formulating granulocyte macrophage colony stimulating factor referenced in Patel et. al., has been shown to only be a stabilizer at acidic conditions and have no effect when formulating at alkaline conditions (see J. Yin, J Chu, M.S Ricci, D. Brems, D Wang, and B. Trout. Effects of Antioxidants on the Hydrogen Peroxide Mediated oxidation of Methionine Residues in Granulocyte Colony Stimulating Factor and Human Parathyroid Hormone Fragment 13-34. *Pharmaceutical Research*. Vol. 21, No. 12, December 2004, IDS filed herewith).

Example 6 provided in the instant patent application shows the advantageous stability profile of the formulation of hGH with methionine and a polyethylene glycol polymer stabilizer as instantly claimed. Applicants respectfully submit that the improved stability profile provides a formulation of hGH that is not suggested by the cited references. For these reasons, Applicants respectfully request the Examiner to reconsider claims 1-15 and withdraw the 35 USC § 103(a) rejection.

Applicants respectfully submit that Claims 1-15 are in condition for allowance. An early and favorable response is respectfully solicited.

Respectfully Submitted:

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